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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,795	11/13/2003	Rosanne Crooke	DOC-0216US	6394

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,795	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *125-145,197-212 and 216-240* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *142-145,197-212,225,227-235,239 and 240* is/are allowed.

6)☒ Claim(s) *125,126,129-141,221-224,226 and 236-238* is/are rejected.

7)☒ Claim(s) *127,128 and 216-220* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 125-145,197-212 and 216-240 are presently pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

3. In the reply filed 10/26/07, Applicants pointed to sequences disclosed in 60/426,234 ('234) to find support for the claimed invention. In particular, Applicants noted the disclosure of SEQ ID NO: 247, and the range of 12 to about 30 disclosed in the '234 application. Therefore, the instant application is considered to have a priority date of November 13, 2002.

Response to Arguments

4. The rejection of claims 125-126 over Hayashi et al. under 35 USC 102(a) is withdrawn in response to Applicant's arguments. The rejection of claims 125-126 and 129-141 under 35 USC 103(a) as being unpatentable over Hayashi et al. in view of Bennett et al. , Dempcy et al. and Simeonov et al. is withdrawn in response to Applicant's arguments presented 10/26/07.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

> only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 125 and 141 are rejected under 35 U.S.C. 102(e) as being anticipated by Almstead et al. (US Patent No. 6,878,729 or US 6,660,737).

7. Almstead et al. discloses an oligonucleotide sequence of 22 bases in length, and comprises 12 contiguous nucleobases of SEQ ID NO: 247. See SEQ ID NO: 11 of Almstead et al. SEQ ID NO: 11 is disclosed as a reverse primer sequence targeting ANP, according to Example V, 300 nM solutions of both the forward and reverse primers are used in reaction mixtures (see col. 31, lines 44-45).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 125, 129-141, and 237-238 are rejected under 35 U.S.C. 103(a) as being unpatentable over Almstead et al. in view of by Bennett et al. (US Patent No. 6172216), Dempcy et al. (US 6,949,367) and Simeonov et al.

The discussion of Almstead et al. as set forth above is incorporated here. However, Almstead et al. does not teach wherein the disclosed oligonucleotides are modified as set forth in the instant claims, or wherein the oligonucleotide is in a sodium salt form.

Bennett et al. teach that the incorporation of modified nucleobases into oligomeric compounds, including 5-methylcytosine modifications, is well known in the

art for the purpose of increasing the binding affinity of the oligomeric compounds of the invention. (col. 9, lines 5-7). Bennett et al. also discloses wherein the oligonucleotide is a chimeric oligonucleotide, comprising 2'-MOE modifications (other positions comprise 2'-deoxy modifications), all 2'-MOE cytosines are 5-methylcytosines, and all linkages are phosphorothioate linkages. Bennett et al. also teach oligomeric compounds of comprising sodium salts, see for example, col. 11, lines 14-23. Additionally, Bennett et al. includes compositions comprising the disclosed oligomeric compounds in combination with a carrier or diluent, see col. 14.

Dempcy et al. teach the use of 2'-O-methoxyethyl modifications in oligonucleotides, wherein the modified oligonucleotides exhibit increased mismatch discrimination (col. 52, lines 2-17).

Simeonov et al. teach the use of oligonucleotide primers bearing locked nucleic acid-modifications in application of allele specific PCR. Simeonov et al. concluded that primer probes bearing LNA modifications have superior properties in the discrimination of single nucleotide variations.

It would have been obvious to the ordinary skilled artisan at the time of the instant invention to combine the teachings of Almstead al., Bennett et al., Dempcy et al. and Simeonov et al. in the making of the claimed invention. One of ordinary skill in the art would have been motivated to make this modification since the oligonucleotides of Almstead al. are disclosed as useful as hybridization probes, and are "specific" for *Enterohemorragic E. coli* O157:H7, and the modifications of Bennett et al. are useful for increasing binding affinity of an oligomer, and Dempcy et al. and Simeonov et al. are

specifically disclosed as useful for increasing the properties of modified oligonucleotides for discrimination of nucleotide variations.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 125-126, and 129-130 are rejected under 35 U.S.C. 102 (b) as being anticipated by Ono et al. (WO 98/36641 A1).

12. Ono et al. discloses a therapeutic composition comprising the oligonucleotide of SEQ ID NO: 9: 5'- TTCT-***GCCTCAGTCTGC***GA-3'. This sequence comprises a 12 base pair contiguous portion of SEQ ID NO: 247 of the instant application. Ono et al. teaches that the oligonucleotides of the invention comprise modifications to improve nuclease resistance and cellular uptake, such as incorporating phosphorothioate residues into the internucleoside backbone (see page 29).

13. The therapeutic compositions of Ono et al. comprise an oligonucleotide and a pharmaceutically acceptable carrier substance (see page 37).

Claim Rejections - 35 USC § 103

14. Claims 125-126, 129-141, 221-223 and 237-238 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ono et al. (as set forth above) in view of Bennett et al. and Wengel et al. (US Patent No. 6,670,461).

15. The teachings of Ono et al. as set forth above are incorporated here. However Ono et al. does not disclose wherein the disclosed therapeutic oligonucleotides comprise 2-O-methoxyethyl modifications, or bi-cyclic 2'-4' sugar modification, wherein the oligonucleotide comprises a 5-methysytosine nucleobase modification, or wherein the oligonucleotide is a chimeric oligonucleotide. Moreover, Ono et al. does not disclose wherein the disclosed therapeutic compositions comprise the penetration enhancer lauric or capric acid.

Bennett et al. teach that the incorporation of modified nucleobases into oligomeric compounds, including 5-methylcytosine modifications, is well known in the art for the purpose of increasing the binding affinity of the oligomeric compounds of the invention. (col. 9, lines 5-7). Bennett et al. also discloses wherein the oligonucleotide is a chimeric oligonucleotide, comprising 2'-MOE modifications (other positions comprise 2'-deoxy modifications), all 2'-MOE cytosines are 5-methylcytosines, and all linkages are phosphorothioate linkages. Bennett et al. also teach oligomeric compounds of comprising sodium salts, see for example, col. 11, lines 14-23. Additionally, Bennett et al. teach the pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. The penetration enhancers of Bennett et al. include for example, oleic acid, lauric acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, and dicaprate see col. 13, lines 10-25).

Additionally, Bennett et al. includes compositions comprising the disclosed oligomeric compounds in combination with a carrier or diluent, see col. 14. The modified therapeutic oligonucleotides of Bennett et al. are disclosed as having increased nuclease stability and increased cellular uptake.

Wengel et al. teach the modification of oligonucleotides to comprise locked nucleosides comprising a bridge between the 2'-O and the 4' carbon atom. Oligonucleotides comprising this modification are described as forming duplexes with higher specificity with its target, and having increased thermostability with its target in comparison to un-modified oligonucleotides.

It would have been obvious to the ordinary skilled artisan to modify the therapeutic oligonucleotides of Ono et al. wit the teachings of Bennett et al. and Wengel et al. One of ordinary skill in the art would have been motivated to make this modification for the known benefits that the modifications taught by both Bennett et al. and Wengel et al. would confer on the oligonucleotides of Ono et al. Specifically, the ordinary skilled artisan would in the art would have had a high expectation that modifying the oligonucleotide of Ono et al. would result in a therapeutic oligonucleotide having both increase nuclease stability, increased cellular uptake, and increased specificity.

Claim Rejections - 35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 224, 226 and 236 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Claims 224, 226 and 236 recite the limitation "at least one additional therapeutic agent," there is insufficient antecedent basis for this limitation in these claims.

Conclusion

19. Claims 127-128, 216-220 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

20. Claims 142-145, 197-212, 225, 227-235, 239-240 are allowable over the prior art searched.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE